PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 453/02, 487/08, 401/06, A61K 31/44, 31/50, 31/505 — A1

(11) International Publication Number: WO 97/11072

(43) International Publication Date: 27 March 1997 (27.03.97)

(21) International Application Number: PCT/DK96/00401

(22) International Filing Date: 20 September 1996 (20.09.96)

(30) Priority Data:
1063/95 22 September 1995 (22.09.95) DK
1166/95 16 October 1995 (16.10.95) DK

(71) Applicant *(for all designated States except US)*: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: OLESEN, Preben, Houlberg [DK/DK]; Ørevadsvej 20, DK-2400 Copenhagen NV (DK). HANSEN, John, Bondo [DK/DK]; Langåsen 3, DK-4450 Jyderup (DK). HANSEN, Holger, C. [DK/DK]; Bringekrogen 9, DK-3500 Værløse (DK).

(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL SUBSTITUTED AZACYCLIC OR AZABICYCLIC COMPOUNDS

(57) Abstract

The present invention relates to therapeutically active heterocyclic compounds, to methods for their preparation and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in treating diseases in the central nervous system related to malfunctioning of the nicotinic cholinergic system.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

Novel Substituted Azacyclic or Azabicyclic Compounds

Field of the Invention

The present invention relates to heterocyclic compounds which are cholinergic ligands selective for neuronal nicotinic channel receptors, to methods for their preparation, to pharmaceutical compositions comprising them, and to their use in treating cognitive, neurological and mental disorders, such as dementia and anxiety, which are characterized by decreased cholinergic function. The invention also relates to a method of treating Parkinson's disease by modulating the process of dopamine secretion, a method of treating or preventing withdrawal symptoms caused by cessation of chronic or long term use of tobacco products, as well as a method for treating obesity.

Background of the Invention

Nicotinic and muscarinic receptors are the two distinct types of cholinergic receptors named after their selectivity for muscarine and nicotine, respectively. The cholinergic system is the neurotransmitter system that best correlates with memory and cognitive functions. Traditionally, the cholinergic hypothesis for senile dementia of the Alzheimer type (SDAT) has focused on muscarinic acetylcholine receptors (mAChR), and only recently an interest in the role of the nicotinic acetylcholine receptors (nAChR) in SDAT has emerged. This interest was spurred by the relatively recent discovery that nAChR are not only located on the skeletal muscle but also in the brain.

It has been shown that the number of nAChR were decreased in SDAT patients (Nordberg et al. J. Neurosci. Res.Vol. 31, pp. 103-111 (1992); Giacobini Advances in Experimental Medicine and Biology, Vol. 296, pp.9205-9295, (1993); Schroeder et al., Neurobiol. of Aging, Vol. 12,

pp. 259-262, (1991); Whitehouse et al., Neurology, Vol. 38, pp. 720-723, (1988); Flynn and Mash, J. Neurochem., Vol. 47, pp. 8702-8702, (1993)). Similar deficiencies in choline acetyltransferase activity and acetylcholine synthesis suggest that presynaptic receptors on cholinergic nerve terminals are preferentially lost in SDAT (Nordberg, J. Reprod. Fert. Suppl., Vol 46, pp. 145-154, (1993)). Therefore, it has been assumed that the loss of nAChR may correlate with age related onset of disorders of memory and cognitive functions, and that nicotinic replacement therapy may prove beneficial in SDAT. Indeed nicotine improved attention and memory in healthy humans (Warburton, Prog. Neuro. Psychopharmacol. Biol.. Psychiatry, Vol. 16, pp. 181-191, (1992)) as well as in Alzheimer's disease patients, (Jones et al. Psychopharmacology, Vol. 108, pp. 485-494, (1992); Gitelman and Prohovnik, Neurobiol. of Aging, Vol. 13, pp. 313-318, (1992); Newhouse et al., Psychopharmacology, Vol. 95, pp. 171-175, (1988); Sahakian et al., Br. J. Psychiatry, Vol.154, pp. 9004-904, (1993)). Further the nicotinic antagonist mecamylamine has been shown to cause cognitive impairment in an age related way, (Newhouse et al., Neuropsychopharmacology, Vol 10, pp. 93-107, (1994)).

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. There is evidence that nicotine may also have beneficial effects in PD. Studies show that smoking may protect against the development of PD, (Ishikawa and Mmiyatake, J. Neurol. Sci., Vol. 117, pp. 28-32, (1993); Godwin-Austen et al., J. Neurol.. Neurosurg. Psychiat., Vol. 45, pp. 577-581, (1982); Reavill, in Nicotine psychopharmacology: Molecular, cellular and behavioral aspects, pp. 307-340, Oxford University Press, (1990)), and that chronic nicotine may protect against cell loss in the substantia nigra caused by lesioning (Janson and Moller, Neuroscience, Vol. 57, 931-941, (1993)). Nicotine has also shown beneficial effects in Tourette's syndrome (Sanberg et al., Biomed. Phamacother., Vol. 43, pp. 19-23, (1989)). Alleviation of negative psychotic symptoms,

known as the hypofrontality syndrome in schizophrenia, by nicotinic agonists, have been suggested by data showing that nicotine stimulates dopamine release in the nucleus accumbens more potently than in striatum, (Rowell et al. J. Neurochem., Vol. 49, pp. 1449-1454, (1987); Giorguieff-Chesselet et al., Life Sciences, Vol. 25, pp. 1257-1262, (1979)), by nicotinic reversal of inactivation of prefrontal neurons (Svenson et al., In the Biology of Nicotine dependence., pp. 169-185, New York, (1990)), and by the observation that nicotine will potentiate dopaminergic effects in various behavioral models, (Reavill, in Nicotine psychopharmacology: Molecular, cellular and behavioral aspects, pp. 307-340, Oxford University Press, (1990); Rosecrans et al., Psychopharmacol. Commmun., Vol. 2, pp. 349-356, (1976); Reavill and Stolerman, J. Psychopharmacol., Vol. 1, pp. 264, (1987)).

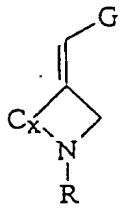
In recent years there have been several studies on the effects of nicotine and food consumption and associated changes in body weight in rat and human. (Greenberg et al., Addictive behaviours, Vol. 7, pp. 317-331, (1982) and Greenberg et al., Psychopharmacology, Vol. 90, pp. 101-105, (1984)). The appetite effects of nicotine have been suggested to be mediated via modulation of CCK peptides in the paraventricular hypothalamic nucleus (Fuxe et al., Acta Physiologica Scandinavica, Vol. 125, pp. 437-443, (1985)).

Description of the invention

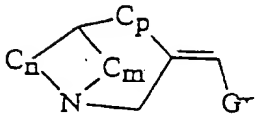
It is an object of the invention to provide novel heterocyclic compounds with affinity and selectivity for nicotinic cholinergic receptors, to methods for their preparation, to pharmaceutical compositions containing them, and to their use in treating Alzheimer's disease, Parkinson's disease, Tourette's syndrome, ulcerative colitis, obesity, other central nervous system and gastrointestinal disorders as well as severe pain.

The present invention relates to novel substituted azacyclic or azabicyclic

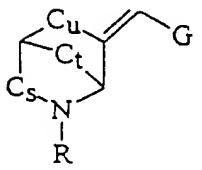
compounds of formula Ia, Ib and Ic selected from the following:



(Ia)



(Ib)



(Ic)

(Ia) (Ib) (Ic)

wherein x is 1,2,3,4 or 5; and

n is 1, 2 or 3; and

m is 1, 2 or 3; and

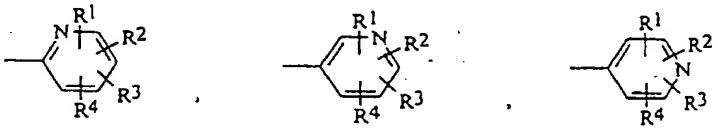
p is 0, 1 or 2; and

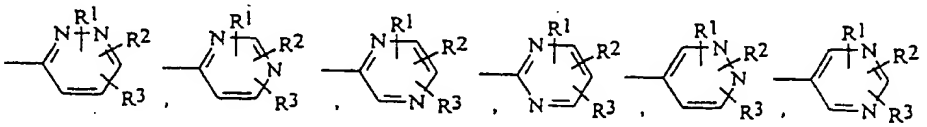
s is 0, 1 or 2; and

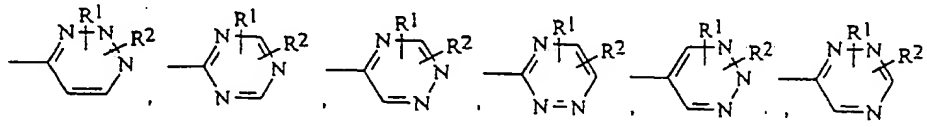
t is 0, 1 or 2; and

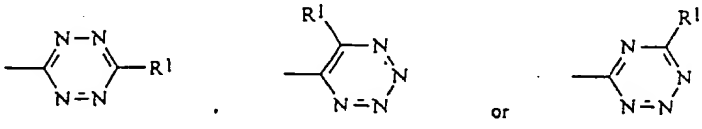
u is 0, 1 or 2; and

R is hydrogen or C_{1-6}-alkyl; and G is selected among the following heterocycles



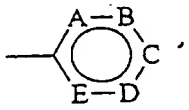






wherein R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, $-NO_2$, -CN, $-OR^5$, $-SR^5$, C_{1-6}-alkyl,C_{1-6}-polyfluoroalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, C_{2-6}-alkoxyalkyl, C_{2-6}-alkylthioalkyl, C_{2-6}-alkylaminoalkyl wherein R^5 is hydrogen or C_{1-6}-alkyl; or a pharmaceutically acceptable salt thereof.

In the following there will also be used another form of presenting G:



wherein -A-B-C-D-E- is selected from $-N=C(R^1)-C(R^2)=C(R^3)-C(R^4)=$, $-C(R^1)=N-C(R^2)=C(R^3)-C(R^4)=$, $-C(R^1)=C(R^2)-N=C(R^3)-C(R^4)=$, $-N=N-C(R^1)=C(R^2)-C(R^3)=$, $-N=C(R^1)-N=C(R^2)-C(R^3)=$, $-N=C(R^1)-C(R^2)=N-C(R^3)=$, $-N=C(R^1)-C(R^2)=C(R^3)-N=$, $-C(R^1)=N-N=C(R^2)-C(R^3)=$, $-C(R^1)=N-C(R^2)=N-C(R^3)=$, $-N=C(R^1)-N=C(R^2)-N=$, $-N=N-N=C(R^1)-C(R^2)=$, $-N=C(R^1)-N=N-C(R^2)=$, $-N=C(R^1)-C(R^2)=N-N=$, $-C(R^1)=N-N=N-C(R^2)=$, $-C(R^1)=N-C(R^2)=N-N=$, $-N=N-C(R^1)=N-N=$, $-C(R^1)=N-N=N-N=$, $-N=C(R^1)-N=N-N=$.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are hereby incorporated by reference.

The compounds of formula I may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallization of suitable salts.

The term "C_{1-3}-alkyl" and "C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having the indicated number of carbons such as for "C_{1-3}-alkyl" methyl, ethyl, n-propyl and isopropyl and for "C_{1-6}-alkyl" methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. butyl, isobutyl, tert. butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 4-methylpentyl, neopentyl, n-hexyl and 2,2-dimethylpropyl and the like.

The term "C_{3-6}-cycloalkyl" as used herein refers to a radical of a saturated cyclic hydrocarbon having from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and the like.

The term "C_{2-6}-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having from 2 to 6 carbon atoms and at least one double bond such as vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl and the like.

"Polyfluoro" in "C_{1-6}-polyfluoroalkyl" means a C_{1-6}-alkyl substituted with from 2 to 13 fluorine atoms such as $-CF_3$, $-CH_2-CF_3$, $-CH_2-CH_2-CF_3$ and $-CH_2-CH_2-CH_2-CF_3$ and the like.

The term "C_{2-6}-alkynyl" as used herein refers to an unsaturated hydrocarbon chain having from 2 to 6 carbon atoms and at least one triple bond such as $-C\equiv CH$, $-CH_2-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-CH(CH_3)C\equiv H$ and the like.

"C_{2-6}-alkoxyalkyl" as used herein means a group of 2 to 6 carbons interrupted by an O such as $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-CH_2-O-CH_2-CH_3$

and the like.

"C_{2-6}-alkylthioalkyl" means a group of 2 to 6 carbons interrupted by an S such as $-CH_2-S-CH_3$, $-CH_2-CH_2-S-CH_3$, $-CH_2-S-CH_2-CH_3$ and the like.

"C_{2-6}-alkylaminoalkyl" means a group of 2 to 6 carbons interrupted by an N such as $-CH_2-NH-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-NH-CH_2-CH_3$ and the like.

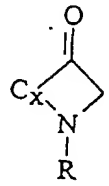
The term "halogen" means fluorine, chlorine, bromine and iodine.

In a preferred embodiment of the invention R represents H or C_{1-3}-alkyl. For x, a preferred value is 2, 3 or 4, n, m and p is preferably respectively 2, 1 and 0 or 2, 2 and 0 or 3, 1 and 0 and s, t and u is preferably respectively 1, 1 and 0 or 1, 2 and 0 or 1, 2 and 1.

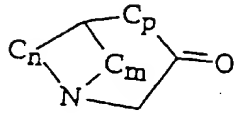
Preferred compounds include:
(Z)-3-(2-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
(Z)-3-(2-Pyrazinylmethylene)-1-azabicyclo[2.2.2]octane;
(Z)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(4-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(4-Pyrimidylmethylene)-1-azabicyclo[2.2.2]octane;
(E)-3-(2-Pyrazinyl)methylene-1-azabicyclo[2.2.2]octane;
(E)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(3-Pyridylmethylene)-1-azabicyclo[2.2.1]heptane;
(E)-3-(3-Pyridylmethylene)piperidine;
(Z)-3-(3-Pyridylmethylene)-piperidine;
or a pharmaceutically acceptable salt thereof.

The invention also relates to a method of preparing the above mentioned compounds of formula I. These methods comprise:

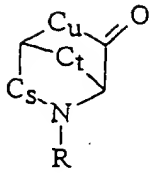
a) reacting a compound of formula II, III or IV



(II)

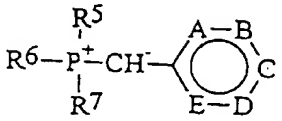


(III)

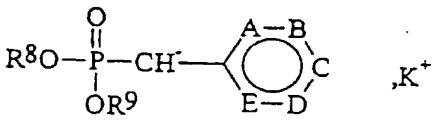


(IV)

wherein x, n, m, p, s, t, u and R have the meanings defined above with a phosphorus ylide of formula V or an alkyl phosphonate of formula VI



(V)

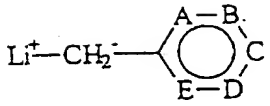


(VI)

wherein -A-B-C-D-E- have the meanings defined above and R^5, R^6, R^7, R^8 and R^9 independently are straight or branched C_{1-6}-alkyl, to give compounds of the general formula Ia, Ib or Ic;

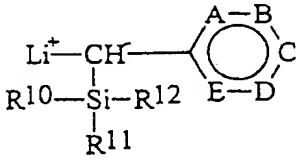
b) reacting a compound of formula II, III or IV with a compound of formula VII

(VII)



wherein -A-B-C-D-E- have the meanings defined above followed by dehydration, to give compounds of the general formula Ia, Ib or Ic; or

c) reacting a compound of formula II, III or IV with a compound of formula VIII



(VIII)

wherein R^{10}, R^{11} and R^{12} independently are straight or branched C_{1-6}-alkyl and -A-B-C-D-E- have the meanings defined above, to give compounds of the general formula Ia, Ib or Ic.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^{3}H-methylcarbamylcholine (^{3}H-MCC) (Abood and Grassi, Biochem. Pharmacol., Vol. 35, pp. 4199-4202, (1986)).

^{3}H-MCC labels the nicotinic receptors in the CNS. The inhibitory effect on ^{3}H-MCC binding reflects the affinity for nicotinic acetylcholine receptors.

Fresh or frozen rat, brain tissue (hippocampus or cortex) was homoge-

nized in assay buffer (50mM Tris-HCl, pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) and centrifuged for 10 min. at 40.000 x g. Pellets were subsequently reconstituted in assay buffer and an appropriate amount of tissue sample was mixed in tubes with ^{3}H-methylcarbamylcholine (NEN, NET-951; final concentration 2 nM) and test drug. The tubes were incubated at 0 °C for 60 min. Unbound ligand was separated from bound ligand by vacuum filtration through GF/B filters presoaked in 0.5 % polyethylenimine. Filters were washed three times with 5 ml wash buffer (50mM Tris-HCl, pH 7.4) and transferred to vials. 4 ml scintillation fluid was added and the radioactivity was measured by scintillation counting. Unspecific binding was measured with 10 µM nicotine.

The IC_{50} values of the test compounds were determined by nonlinear regression analyses (GraphPad InPlot).

Furthermore, the pharmacological properties of the compounds of the invention can also be illustrated by determining their capability to inhibit the specific binding of ^{3}H-Oxotremorine-M (^{3}H-Oxo). Birdsdall N.J.M., Hulme E.C., and Burgen A.S.V. (1980). "The Character of Muscarinic Receptors in Different Regions of the Rat Brain". Proc. Roy. Soc. London (Series B) 207,1.

^{3}H-Oxo labels muscarinic receptor in the CNS (with a preference for agonist domains of the receptors). Three different sites are labelled by ^{3}H-Oxo. These sites have affinity of 1.8, 20 and 3000 nM, respectively. Using the present experimental conditions only the high and medium affinity sites are determined.

The inhibitory effects of compounds on ^{3}H-Oxo binding reflects the affinity for muscarinic acetylcholine receptors.

All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-250 g) is homogenized for 5-

10 s in 10 ml 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 10 ml of buffer and the combined suspension centrifuged for 15 min. at 40,000 x g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 2 x 10 ml of buffer and centrifuged for 10 min. at 40,000 x g.

The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 ml per g of original tissue) and used for binding assay. Aliquots of 0.5 ml is added 25 ul of test solution and 25 ul of ^{3}H-Oxotremorine (1.0 nM, final concentration) mixed and incubated for 30 min. at 25°C. Non-specific binding is determined in triplicate using arecoline (1 ug/ml, final concentration) as the test substance. After incubation samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 ml of ice-cold buffer. The amount of radioactivity on the filters are determined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding.

Test substances are dissolved in 10 ml water (if necessary heated on a steam-bath for less than 5 min.) at a concentration of 2.2 mg/ml. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50}. The test value will be given as IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of ^{3}H-Oxo by 50%).

IC_{50} = (applied test substance concentration) $x(C_x/C_o-C_x)$nM

where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Table I illustrates the affinity of the compounds of the present invention for nicotinic and muscarinic receptors as determined by ^{3}H-MCC and ^{3}H-Oxo binding to rat cortical receptors. The compounds, however, show

selective affinity for nicotinic receptors as compared to muscarinic receptors, i.e OXO/MCC > 1.

Table 1

Compound	^{3}H-MCC IC_{50} nM	^{3}H-Oxo IC_{50} nM	Oxo/MCC Ratio
1	> 300	<1000	-
2	180	720	4
3	4.2	890	212

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 10 mg to about 70 mg per day. In choosing a regimen for patients suffering from diseases in the central nervous system caused by malfunctioning of the nicotinic cholinergic system it may frequently be necessary to begin with a dosage of from about 30 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intraurethral, intramuscular, topical, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

Typical compositions include a compound of formula Ia, Ib or Ic or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semisolid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit

dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph. Eur.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

(Z)-3-(2-Pyridylmethylene)-1-azabicyclo[2.2.2]octane dioxalate

A 2.5 M solution of n-butyllithium in hexane (3.4 ml, 8.5 mmol) was added over 5 min to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.19 g, 8.5 mmol) in 10 ml of dry tetrahydrofuran (THF) under nitrogen in a reaction vessel cooled in a dry ice/isopropyl alcohol bath at -75°C. The mixture was stirred for 10 min. To the resulting solution of lithium tetramethylpiperidine (LTMP), 2-trimethylsilylmethylpyridine (1.4 g, 8.5 mmol) was added dropwise over 10 min. After stirring for 10 min a solution of 3-quinuclidinone (1.8 g, 14 mmol) in 5 ml of THF was added over 15 min. Stirring was continued at -75°C for 1 h. Then the mixture was allowed to warm to room temperature with stirring during 1/2 h, and 25 ml of water was added. The mixture was extracted with three 25 ml portions of diethylether. The extracts were combined and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave 1.55 g of a slowly crystallizing oil. The crystals were collected by filtration

yielding 0.64 g (38%) of (Z)-3-(2-pyridylmethylene)-1-azabicyclo[2.2.2]-octane. M.p. 76-78°C. ^{1}H NMR δ 8.65-8.55 (m, 1H), 7.7-7.5 (m, 1H), 7.2-7.0 (m, 2H), 6.35-6.2 (m, 1H, C=CH-), 4.15-4.0 (m, 2H, N-CH_2C=), 3.1-2.8 (, 4H, N-CH_2-C), 2.6-2.45 (m, 1H, methin),2.0-1.7 (m, 4H, C-CH_2-C).

To a solution of (Z)-3-(2-pyridylmethylene)-1-azabicyclo[2.2.2]octane (0.5 g) in 4 ml of acetone was added with stirring at room temperature a solution of oxalic acid (0.7 g) in 3 ml of acetone. An additional 7 ml of acetone was added and the mixture was stirred for 1 h. The precipitate was filtered off and dried to give 1.0 g (100%) of the title compound as a white powder. M.p. 162-164°C. (Compound 1).

EXAMPLE 2

The following compounds were prepared in the same manner as the Peterson reaction described in Example 1. In cases where both (E) and (Z) isomers of the alkene were formed, the isomers could be separated by column chromatography on silica gel using a mixture of dichloromethane-/methanol/aqueous ammonia (80:20:1/2) as eluent.

(Z)-3-(2-Pyrazinyl)methylene-1-azabicyclo[2.2.2]octane trioxalate starting from 2-trimethylsilylmethylpyrazine, LTMP, and 3-quinuclidinone. M.p. 147-152°C. (Compound 2).

(Z)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane dioxalate starting from 3-trimethylsilylmethylpyridine, lithium diisopropylamide (LDA), and 3-quinuclidinone. M.p. 197-200°C. (Compound 3).

3-(4-Pyridylmethylene)-1-azabicyclo[2.2.2]octane dioxalate starting from 4-trimethylsilylmethylpyridine, LTMP, and 3-quinuclidinone. M.p. 185-

188°C (melts partially at 142°C). (Compound 4).

3-(4-Pyrimidylmethylene)-1-azabicyclo[2.2.2]octane oxalate starting from 4-trimethylsilylmethylpyrimidine, LTMP, and 3-quinuclidinone. M.p. 140-145°C. (Compound 5).

(E)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane dioxalate, starting from 3-trimethylsilylmethylenepyridine, lithiumdiisopropylamine (LDA) and 3-quinuclidinone. Compound 7. Mp 145-146 °C.

EXAMPLE 3

(E)-3-(2-Pyrazinyl)methylene-1-azabicyclo[2.2.2]octane oxalate

To a solution of diisopropylamine (2.02 g, 20 mmol) in tetrahydrofuran (50 ml) was added butyllitium (2.5 M in hexanes, 8 ml, 20 mmol). The reaction mixture was stirred at 0°C for 30 min. then cooled to -78 °C. 2-Methylpyrazine (1.88 g, 20 mmol) in tetrahydrofuran (10 ml) was added and the reaction mixture was stirred for 1 hour at -78°C. Quinuclidinone (3.75 g, 30 mmol) in tetrahydrofuran (10 ml) was added and the reaction mixture was stirred for another 1 hour at -78°C, then slowly heated to 0°C and stirred at this temperature for 0.5 hour. Triethylamine (4.5 g, 50 mmol) and thionyl chloride (8.0 g, 68 mmol) was added, and the reaction mixture was stirred for 0.5 hour. The reaction mixture was quenched with water (150 ml) and acidified with concentrated hydrochloric acid. The water phase was extracted with ether (2 x 50 ml) then basified with solid potassium carbonate and extracted with ether (4 x 100 ml). The basic ether extracts were combined, dried over magnesiumsulphate and evaporated. The crude compound was crystallized as the oxalate salt from ethanol giving the title compound in 10 % yield. M.p. 149-150°C. (Compound 6).

EXAMPLE 4

3-(3-Pyridylmethylene)-1-azabicyclo[2.2.1]heptane dioxalate

To a solution of diisopropylamine (1.15 ml, 8.0 mmol) in tetrahydrofuran (25 ml) was added butyllitium (1.6 M, 5 ml, 8 mmol). The mixture was stirred for 45 min at 0 °C, and 3-tertbutyldimethylsilylmethylenepyridine (1.7 g, 8 mmol) dissolved in tetrahydrofuran (5 ml) was added. The reaction mixture was stirred for 45 min., then cooled to -60 °C , and 1-azabicyclo[2.2.1]heptan-3-one (0.85 g, 7.6 mmol dissolved in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred at -60 °C for 1.5 hours, then quenched with water (100 ml), and made alkaline with solid potassium carbonate. The water phase was extracted with ether (3x75 ml). The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica (eluent : methanol/ethylacetate/ammoniumhydroxide 25%: 1:2:0.02). The product was isolated as a mixture of (Z) and (E) isomers in the relative proportion 2:1. The free base was crystallised as the oxalic acid salt from acetone in 45 % (770 mg) yield. Compound 8. Mp. 162-65 °C.

EXAMPLE 5

1-Benzyl-3-(3-pyridylmethylene)piperidine

To a solution of diisopropylamine (1.5 ml, 10.0 mmol) in tetrahydrofuran (40 ml) was added butyllithium (1.6 M, 6.3ml, 10 mmol). The mixture was stirred for 45 min at 0 °C, and 3-tertbutyldimethylsilylmethylene-pyridine (2.1 g, 10 mmol) dissolved in tetrahydrofuran (5 ml) was

added. The reaction mixture was stirred for 45 min., then cooled to -60 °C , and 1-benzyl-3-piperidone (2.3 g, 10.0 mmol) dissolved in tetrahydrofurane (10 ml) was added. The reaction mixture was stirred at -60 °C for 1.5 hours, then quenched with water (100 ml). The water phase was extracted with ether (3x75 ml). The combined organic extracts were dried over magnesiumsulfate and evaporated. The residue was purified by column chromatography on silica (eluent: ethylacetate). The first fractions contained the (Z)-benzyl-3-(3-pyridylmethylene)piperidine isomer, which was isolated in 25 % (650 mg) yield. The next fractions contained the (E)-benzyl-3-(3-pyridylmethylene)piperidine isomer, which was isolated in 23 % (600 mg) yield.

EXAMPLE 6

(E)-3-(3-Pyridylmethylene)piperidine

To a solution of (E)-benzyl-3-(3-pyridylmethylene)piperidine (600 mg, 2.3 mmol) in toluene (30 ml) was added 1-chloroethyl chloroformate (0.38 ml, 3.5 mmol). The reaction mixture was heated at 100 °C for 1 hour, then evaporated. Methanol (25 ml) was added, and the reaction mixture was heated at reflux for 1 hour. The reaction mixture was evaporated and water (100 ml) was added. The water phase was made alkaline with solid potassium carbonate and extracted with ethylacetate (3 x 50 ml). The combined organic extracts were dried over magnesiumsulfate and evaporated. The residue was purified by column chromatography on silica (eluent: methanol/ethylacetate/ammoniumhydroxide 25%: 1:2:0.02). The free base was crystallised as the oxalic acid salt from acetone. Yield 90 mg (15 %). Compound 9. Mp 133-34 °C.

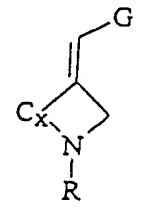
EXAMPLE 7

(Z)-3-(3-Pyridylmethylene)piperidine dihydrochloride

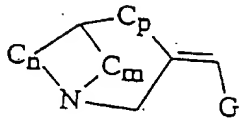
To a solution of (Z)-benzyl-3-(3-pyridylmethylene)piperidine (650 mg, 2.4 mmol) in toluen (30 ml) was added 1-chloroethyl chloroformate (0.40 ml, 3.7 mmol). The reaction mixture was heated at 100 °C for 4 hours, then evaporated. Methanol (25 ml) was added, and the reaction mixture was heated at reflux for 1 hour. The reaction mixture was evaporated and water (100 ml) was added. The water phase was made alkaline with solid potassium carbonate and extracted with ethylacetate (3 x 50 ml). The combined organic extracts were dried over magnesiumsulfate and evaporated. The residue was purified by column chromatography on silica (eluent: methanol/ethylacetate/ammoniumhydroxide 25%: 1:2:0.02). The free base was crystallised as the hydrochloric acid salt from acetone. Yield 60 mg (14 %). Compound 10. Mp 218-21 °C.

CLAIMS

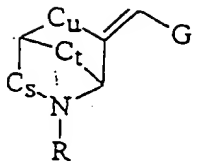
1. A compound of formula Ia, Ib or Ic



(Ia)



(Ib)



(Ic)

wherein x is 1,2,3,4 or 5; and

n is 1, 2 or 3; and

m is 1, 2 or 3; and

p is 0, 1 or 2; and

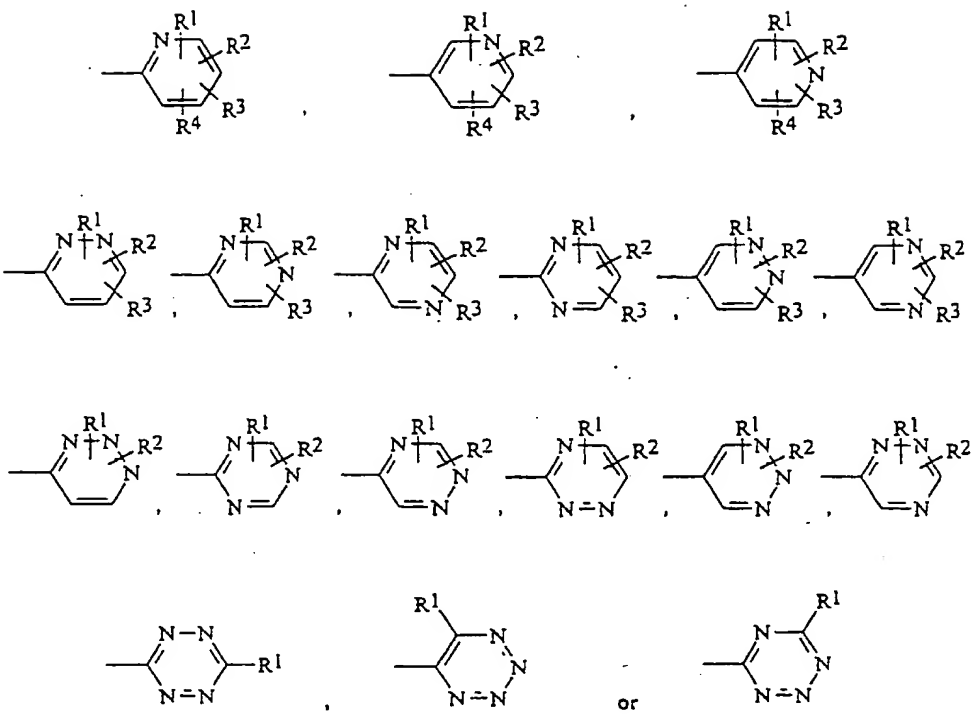
s is 0, 1 or 2; and

t is 0, 1 or 2; and

u is 0, 1 or 2; and

R is hydrogen or C_{1-6}-alkyl; and

G is selected among the following heterocycles



wherein R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, $-NO_2$, -CN, $-OR^5$, $-SR^5$, C_{1-6}-alkyl,C_{1-6}-polyfluoroalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, C_{2-6}-alkoxyalkyl, C_{2-6}-alkylthioalkyl, C_{2-6}-alkylaminoalkyl wherein R^5 is hydrogen or C_{1-6}-alkyl; or a pharmaceutically acceptable salt thereof.

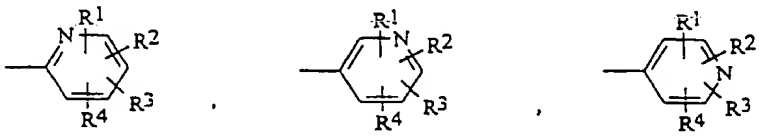
2. A compound according to claim 1 wherein R is H or C_{1-3}-alkyl.

3. A compound according to anyone of the preceding claims wherein x is 2, 3 or 4.

4. A compound according to anyone of the preceding claims wherein n, m and p is respectively 2, 1 and 0 or 2, 2 and 0 or 3, 1 and 0.

5. A compound according to anyone of the preceding claims wherein s, t and u is respectively 1, 1 and 0 or 1, 2 and 0 or 1, 2 and 1.

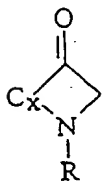
6. A compound according to anyone of the preceding claims wherein G is selected from the following heterocycles



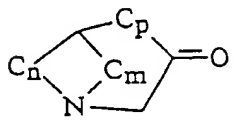
7. A compound according to claim 1, wherein the compound is selected from the following:
(Z)-3-(2-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
(Z)-3-(2-Pyrazinylmethylene)-1-azabicyclo[2.2.2]octane;
(Z)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(4-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(4-Pyrimidylmethylene)-1-azabicyclo[2.2.2]octane;
(E)-3-(2-Pyrazinyl)methylene-1-azabicyclo[2.2.2]octane;
(E)-3-(3-Pyridylmethylene)-1-azabicyclo[2.2.2]octane;
3-(3-Pyridylmethylene)-1-azabicyclo[2.2.1]heptane;
(E)-3-(3-Pyridylmethylene)piperidine;
(Z)-3-(3-Pyridylmethylene)-piperidine;
or a pharmaceutically acceptable salt thereof.

8. A method of preparing a compound according to claim 1, CHARACTERIZED IN

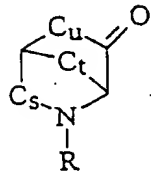
a) reacting a compound of formula II, III or IV



(II)

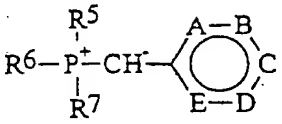


(III)

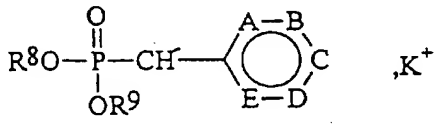


(IV)

wherein x, n, m, p, s, t, u and R have the meanings defined above with a phosphorus ylide of formula V or an alkyl phosphonate of formula VI.



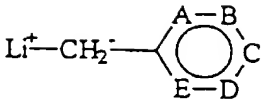
(V)



(VI)

wherein -A-B-C-D-E- is selected from $-N=C(R^1)-C(R^2)=C(R^3)-C(R^4)=$, $-C(R^1)=N-C(R^2)=C(R^3)-C(R^4)=$, $-C(R^1)=C(R^2)-N=C(R^3)-C(R^4)=$, $-N=N-C(R^1)=C(R^2)-C(R^3)=$, $-N=C(R^1)-N=C(R^2)-C(R^3)=$, $-N=C(R^1)-C(R^2)=N-C(R^3)=$, $-N=C(R^1)-C(R^2)=C(R^3)-N=$, $-C(R^1)=N-N=C(R^2)-C(R^3)=$, $-C(R^1)=N-C(R^2)=N-C(R^3)=$, $-N=C(R^1)-N=C(R^2)-N=$, $-N=N-N=C(R^1)-C(R^2)=$, $-N=C(R^1)-N=N-C(R^2)=$, $-N=C(R^1)-C(R^2)=N-N=$, $-C(R^1)=N-N=N-C(R^2)=$, $-C(R^1)=N-C(R^2)=N-N=$, $-N=N-C(R^1)=N-N=$, $-C(R^1)=N-N=N-N=$, $-N=C(R^1)-N=N-N=$ and R^5, R^6, R^7, R^8 and R^9 independently are straight or branched C_{1-6}-alkyl, to give compounds of the general formula Ia, Ib or Ic;

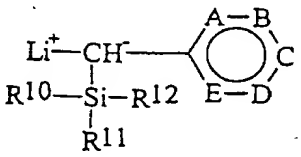
b) reacting a compound of formula II, III or IV with a compound of formula VII



(VII)

wherein -A-B-C-D-E- have the meanings defined above, followed by dehydration, to give compounds of the general formula Ia, Ib or Ic; or

c) reacting a compound of formula II, III or IV with a compound of formula VIII



(VIII)

wherein R^{10}, R^{11} and R^{12} independently are straight or branched C_{1-6}-alkyl and -A-B-C-D-E- have the meanings defined above, to give compounds of the general formula Ia, Ib or Ic.

9. A pharmaceutical composition comprising as active component a compound according to anyone of claims 1 to 7 together with a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition suitable for treating a disease in the central nervous system related to malfunctioning of the nicotinic cholinergic system comprising an effective amount of a compound according to anyone of claims 1 to 7 together with a pharmaceutically acceptable carrier or diluent.

11. The pharmaceutical composition according to claim 9 or 10 in the form of an oral dosage unit or parenteral dosage unit.

12. The pharmaceutical composition according to claim 11, wherein said dosage unit comprises from about 1 to about 100 mg of the compound according to anyone of claims 1 to 7.

13. A method of treating a central nervous system ailment related to malfunctioning of the nicotinic cholinergic system in a subject in need of such treatment comprising administering to said subject an effective amount of a compound according to anyone of claims 1 to 7.

14. A method of treating a central nervous system ailment related to malfunctioning of the nicotinic cholinergic system in a subject in need of such treatment comprising administering to said subject a pharmaceutical composition according to anyone of claims 9 to 12.

15. The use of a compound according to anyone of claims 1 to 7 for the preparation of a medicament for treatment of a disease in the central nervous system related to malfunctioning of the nicotinic cholinergic system.

Our ref: 4532-WO,LaKe

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00401

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 453/02, C07D 487/08, C07D 401/06, A61K 31/44, A61K 31/50, A61K 31/505
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Volume 123, No 11, 11 Sept 1995 (11.09.95), (Columbus, Ohio, USA), page 130, THE ABSTRACT No 132885k, JP, 761940, A, (Akasaka, Kozo et al) 7 March 1995 (07.03.95) --	1-12,15
A	EP 0414394 A2 (BEECHAM GROUP P.L.C.), 27 February 1991 (27.02.91) --	1-12,15
A	EP 0638569 A1 (KANEGAFUCHI KAGAKU KOGYO KABUSHIKI KAISHA), 15 February 1995 (15.02.95) --	1-12,15
A	US 3852279 A (JOHN KRAPCHO ET AL), 3 December 1974 (03.12.74), see example 13 --	1-12,15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 1996	14 -12- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00401

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13 and 14
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						